Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION
44 EAST 23RD STREET, NEW YORK 10, N. Y.

Editor
HOWARD P. LEWIS, M.D.
Portland, Ore.

Associate Editor
HERBERT E. GRISWOLD, JR., M.D.
Portland, Ore.

Associate Editor
FRANKLIN J. UNDERWOOD, M.D.
Portland, Ore.

Copyright 1960 by the American Heart Association, Inc.

Vol. XXIX **APRIL, 1960** **No. 4**

TREATMENT OF HYPERTENSION*

Attitudes toward hypertensive cardiovascular disease have changed in the past several years. This change has been due to three factors: (1) development of antihypertensive drugs of long-term effectiveness; (2) lively research efforts, increasingly productive of information concerning mechanisms of blood pressure regulation; and (3) recognition of 2 more types of secondary hypertension (primary aldosteronism and occlusive renal artery disease).

Currently, the best approach to the hypertensive patient's problem is to use all means available to discover the cause and severity of the hypertensive disease and then to decide whether treatment is necessary. Since in most patients a cause will not be defined, drug therapy may be indicated. As antihypertensive drugs have been used increasingly, uncertainty has developed concerning the selection of patients to treat, the choice of drug or drugs, whether to recommend surgical sympathectomy, and what can be expected from long-term treatment. The following discussion is a review of the current treatment of hypertension, the pharmacology of antihypertensive drugs and the implications that derive from their use.

* From the Research Division, Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Consequences of Hypertension — Results and Goals of Therapy

Evaluation of treatment of any disease depends, in large part, on an intimate knowledge of its nature and clinical course. As concerns hypertension, the clinical problem ranges from minimal hypertension without obvious signs of arteriolar disease to fulminant malignant hypertension. The consequences of these "benign" and malignant hypertensions are quite different. On the one hand, those of "benign" nature usually do not reflect directly the underlying arteriolar disease but, rather, the associated arterial disease. The most frequent complications result from such atherosclerotic complications as stroke, coronary occlusion, dissection of aortic aneurysms,

ANNUAL MEETING AND 33RD SCIENTIFIC SESSIONS
AMERICAN HEART ASSOCIATION

October 21-23, 1960 **St. Louis, Mo.**

ABSTRACTS for these sessions should be submitted on special forms obtainable from Dr. F. J. Lewy, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Space for **SCIENTIFIC EXHIBITS** may also be requested on special forms available at the address above.

The deadline for all applications is June 1, 1960.

(Registration and hotel reservation form will be included in the May issue.)

or thrombosis of peripheral arteries. Cardiac failure is common, and this may reflect, in part, the arteriolar disease, but renal failure is rare. Arterial disease, associated with "benign" hypertension, can be present for years, not apparently endangering health, but always carrying with it a threat of premature death or disability.

On the other hand, malignant hypertension has consequences directly reflecting the arteriolar disease. These are hypertensive encephalopathy and intracerebral hematoma, exudative and hemorrhagic retinopathy with papilledema, cardiac failure and malignant nephrosclerosis with renal failure. Untreated, malignant hypertension is rapidly fatal. In the series reported by Keith, Wagener and Barker,[1] 80 per cent of the patients were dead within a year after the diagnosis was established.

Drugs have been employed for too brief a period to warrant a serious evaluation of their effectiveness in "benign" essential hypertension. Such an evaluation can only be made from large groups of patients followed for many years.

Because malignant hypertension is rapidly fatal, an evaluation of the effectiveness of drug treatment is justified at this time. The available reports give ample evidence that antipressor therapy can reverse the malignant hypertensive syndrome and considerably prolong life. Our experience[2] shows that patients with good renal function prior to treatment have a good prognosis (at least in terms of survival for several years) and that even those with poor renal function initially may live for years but die of renal failure. Good blood pressure control, while seeming to protect patients from cerebral hemorrhage, does not prevent, although it may slow, progression of coronary, aortic, renal, and peripheral arteriosclerosis. To reverse the malignant hypertensive syndrome, arterial pressure must be reduced, since poor blood pressure control seems merely to attenuate the natural course of the arteriolar disease. The fact that strokes and myocardial infarction occur in patients with good blood pressure control suggests that once arterial damage has occurred, it can progress even though arterial pressure is maintained at much lower, and occasionally normal, levels. Since normal pressure levels are usually not obtained with drug administration, we cannot say with certainty that normotension does not protect previously hypertensive patients from progression of arteriosclerosis. Such information will come from prolonged observation of the relatively few patients in whom normotension can be maintained for years.

Considering the consequences of "benign" essential and malignant hypertension and what we know of the effectiveness of long-term treatment in the latter type, the purpose of medical and surgical antihypertensive treatment can be stated as follows: (1) to reduce arterial pressure to normal or near normal levels in both supine and standing positions; (2) to control or prevent the consequences of arteriolar disease; and (3) to prevent the advance of arteriosclerosis.

Most Commonly Used Antihypertensive Drugs

Ganglion-blocking agents are the most potent antipressor drugs commonly used, since they can lower arterial pressure in hypertensive patients. The first drugs to be developed were quaternary ammonium compounds; later ones were secondary or tertiary amines. The early ones were absorbed poorly from the gastrointestinal tract and had a short period of action. As structure was changed, absorption became better and action longer. These drugs are ganglion-blocking agents because they reduce the transmission of impulses through the ganglia by inhibiting acetylcholine competitively; this effect is called "ganglion blockade." Both sympathetic and parasympathetic ganglia are affected and it is parasympathetic blockade that causes troublesome side effects and limits the amounts of these drugs that can be given.

In animals, complete sympathetic blockade is difficult to achieve and to approach it requires a higher dosage than could ever be used in hypertensive patients. In clinical situations, the partial blockade obtained allows transmission of some impulses, but not all. The powerful neurogenic stimuli maintaining arterial pressure during standing and hemorrhage are the more affected. This explains orthostatic hypotension without a similar decrease of supine blood pressure and the ability of ganglion-blocking drugs to intensify hemorrhagic hypotension.[3]

Physicians administering ganglioplegics should have a knowledge of their effective doses, duration of action, side effects and measures to counteract these side effects. Attempts have been made to produce drugs with lesser parasympathetic blockade, and advertising claims of each new ganglioplegic drug stress freedom from these side effects. These attempts have been partly successful, but it must be remembered that physicians have become more skillful in administering these drugs and that there is individual variation among patients as to which parasympathetic functions are more affected. Thus, a side effect absent in one patient receiving a particular ganglioplegic may be unbearable in another.

Ganglioplegics should be given only when they can be administered in adequate dosage. This can be accomplished through the use of blood pressure measurements prior to each dose and

with dosage adjustments made according to the level of standing systolic blood pressure. Without blood pressure measurements, most patients take insufficient amounts because, aware of the capriciousness of drug absorption, they are justifiably afraid of overdosage. Ganglion-blocking drugs should be reserved for use in patients who will follow the demanding therapeutic regimens and by physicians who are willing to take the time to understand the action of these drugs and the proper method of their administration.

Reserpine. The root of Rauwolfia serpentina contains several alkaloids that modify vasoregulatory reflexes. Of these, reserpine is most active. Prior to the development of oral diuretics, reserpine was the most widely used antihypertensive drug. It is an effective antipressor agent, but it can cause serious mental depression leading to suicide. In our experience, deep depression does not occur without warning and is always preceded by recognizable depressive symptoms; these can be anticipated and the drug stopped before serious trouble develops.

The pharmacologic effects of reserpine seem to be due to a depletion of catecholamines and serotonin in the brain and of noradrenalin in sympathetic nerves and vessel walls. The mental depression may occur because of central depletion of these neurohumors. The hypotensive effect could be due, not only to suppression of activity of the vasomotor center,[4] but also to decreased ability of the sympathetic nerves to form the noradrenalin necessary for vasoconstriction.

If the mechanism of action of reserpine is the same in man as in animals, there is a pharmacologic basis for the clinical experience that reserpine, when given to patients receiving ganglion blockers, often results in further decreases of arterial pressure. Further, as concerns clinical use, it seems advisable to administer small doses, such as 0.25 mg. per day, in order to avoid mental depression and nasal stuffiness. The latter may be extremely troublesome and is counteracted successfully only by locally applied vasoconstrictor agents.

Guanethidine and Bretylium Tosylate. The continuing search for drugs that depress the activity of the sympathetic nervous system while not affecting parasympathetic activity has recently resulted in the release of 2 drugs for clinical trial: guanethidine (Ismelin) and bretylium tosylate (Darenthin). While neither has been studied long enough to establish its scope of usefulness, they are worthy of comment here because each seems to act, at least in part, by decreasing noradrenalin release at the nerve endings.[5,6] Like ganglion-blocking agents, guanethidine and bretylium tosylate cause orthostatic hypotension which can occur without decreases in supine blood pressure. Unlike ganglioplegics, these new compounds do not paralyze parasympathetic ganglia and this is their advantage.

Oral Diuretics. The antipressor potential of adequate low-sodium dietotherapy is as impressive as that of any antihypertensive drug, but the routine use of such diets is more demanding than most patients and physicians can tolerate. Although used extensively in the 1940's, such treatment was practically discarded when potent antihypertensive drugs became available. Prior to this, clinical studies had shown that sodium restriction causes negative salt and water balances but had failed to relate these negative balances to therapeutic responses. A clinical impression existed also that these diets enhanced responsiveness to ganglion-blocking agents.

Chlorothiazide likewise causes negative salt and water balances and when first used was found to increase the effectiveness of the conventional antihypertensive drugs. Since the first clinical trials, considerable investigation to elucidate the mechanism of action of this potent diuretic and its relative, hydrochlorothiazide, has taken place. These studies have shown that the early effects are related to losses of salt and water. A few days' administration results in decreased plasma and extracellular fluid volumes, decreased cardiac output, increased peripheral resistance, decreased pressor responses to noradrenalin and increased depressor responses to ganglion-blocking drugs and trimethapan.[7,8] The changes in vascular reactivity can be obliterated by infusion of salt-free dextran. Thus, the first effects of diuretics seem dependent upon a decrease in intravascular volume but the prolonged effects are probably due to some other mechanism.

Chlorothiazide is, of itself, not a potent antihypertensive drug, but some patients obtain substantial decreases in blood pressure when it is given as the only drug. Our experience is that the higher the blood pressure, the less the likelihood of a good response. Other experience has shown that patients with severe essential or malignant hypertension respond poorly.

Like all of the antihypertensive drugs, oral diuretics are potentially dangerous; they can cause serious hypokalemia which, in patients receiving digitalis, is a hazard. For this reason, it is wise to use as low doses as possible, or intermittent therapy for 3 to 5 consecutive days per week. Some physicians advise potassium supplements, but in these days of polypharmacy, another medicine for the patient to take should be avoided if possible.

Hydralazine is probably the most interesting of the antihypertensive drugs. It is extremely effective in some patients by mechanisms yet unknown. It may cause, usually after many months of therapy, a syndrome clinically indistinguishable from acute disseminated lupus erythema-

tosus. Hydralazine decreases total peripheral resistance, not through any known effect on neurogenic reflexes, but through some peripheral action. It does not change noradrenalin responses significantly; therefore, there is no suggestion that it depletes vessel walls or nerve endings of this neuro-effector. It is the only antihypertensive agent that increases renal blood flow, but this increase seems to have little to do with the clinical effectiveness.

Early side effects of hydralazine are troublesome and are the greatest barrier to its administration. These include tachycardia, with palpitations and headache. The latter is thought to be a histamine effect because hydralazine can inhibit histaminase and the headaches can be relieved by Benadryl, a weak antihistaminic drug. These side effects can cause acute discomfort and have forced some physicians to discontinue the drug before a response was obtained. Such early problems of administration should not obscure the therapeutic gains that may be accomplished if the patient and physician can "cling to the pillars until the storm has passed."

Little is known about the late complications of treatment as seen in the rheumatic and febrile syndrome simulating disseminated lupus erythematosus. The illness usually disappears promptly when the drug is stopped, but occasionally ACTH and adrenal steroids have to be given. It appears more frequently in patients taking large doses and accordingly we do not give more than 200 mg. a day for prolonged periods of time. The possibility of this complication does not prohibit the use of the drug when the patient can be seen frequently.

Combined therapy is the rule of the day. This is unfortunate because all drugs should be used in such a fashion that individual effectiveness is established. Actually, there is a pharmacologic basis for combining a ganglioplegic with reserpine or chlorothiazide, or both. Certainly this cook-book approach will persist until there is a better understanding of the mechanisms of hypertension.

Importance of Pretreatment Evaluation

Proper therapy of hypertension depends upon etiologic diagnosis and estimation of the severity of the vascular disease. For example, it is poor judgment to treat, unwittingly, a patient with coarctation of the aorta as if he had essential hypertension, or to treat mild essential hypertension as if it were malignant. The finding that hypertension is due to one of the known causes usually means a therapeutic approach different from that indicated for essential hypertension; thoracic aortic coarctation, occlusive renal artery disease, tumors of the adrenal cortex or medulla are, as a rule, treated surgically. Definition of the severity of disease and rate of progression dictates not only the type of treatment, but also the rapidity with which the arterial pressure should be lowered. For the patient with stable, uncomplicated hypertension, there is no urgency. For those with hypertensive crises or rapidly advancing malignant hypertension, reduction of arterial pressure within a few hours or days is imperative. The drugs of choice are those known to act rapidly.

Selection of Patients for Treatment

Most patients with high blood pressure have essential hypertension, but since the disease is so varied it is difficult to know which patients warrant treatment. A recent actuarial report gives evidence that even those patients with "high normal" arterial pressure levels are more prone to vascular disease than those with "low normal" levels. This information supports the earlier actuarial experience[9] that even hypertension of mild degree shortens the life span and the clinical experience[10] that, in a large group of hypertensive patients, decreased survival was a function of increasing arterial pressure levels.

One conclusion that could be drawn from these reports is that all hypertensive patients should be treated. However, such enthusiasm seems unwarranted at this time, since all antihypertensive drugs are potentially dangerous, many are difficult to administer, and most can be unpleasant for the patient to take. Further, it should be reemphasized that there is, as yet, no real evidence that the maintenance of arterial pressure at normal levels will prolong the lives of patients with mild hypertension. Until such information is available, the wholesale treatment of the hypertensive population seems unjustified.

What patients, then, should be treated? Certainly not the elderly with systolic hypertension only, nor the patients with mild diastolic hypertension who have family histories of hypertension coupled with long life, nor the middle-aged women who have no signs of vascular disease because women are known to develop fewer hypertensive complications than men. However, if the patient is a man with diastolic hypertension and minimal evidences of vascular disease, he should receive treatment regardless of his family history. So likewise should any patient, even one with mild arterial hypertension, who has a family history of hypertension and of premature death or disability. All patients with signs of progressive vascular disease warrant treatment.

Selection of Drugs

There are no hard or fast rules about antihypertensive drug treatment. As mentioned earlier, initial treatment depends upon a careful

evaluation of the severity of the hypertensive cardiovascular disease and the rapidity with which the arterial pressure should be lowered. For the patients with mild disease, it is justifiable to try first the drugs that are simplest to administer, such as reserpine and/or chlorothiazide. For the patients with congestive cardiac failure or malignant hypertension, a ganglion-blocking drug seems the agent of choice, since these drugs are more predictably depressor and cause venous pooling and decreased venous return to the heart, which is beneficial in the case of cardiac failure. For hypertensive encephalopathy, intravenous nitroprusside is amazingly effective. Hydralazine can be administered in any type of hypertensive disease.

Surgical Treatment

Patients with pheochromocytoma should be treated surgically. Even if it were possible to control the hypertension with adrenergic blocking agents, the tumors should be removed because they can undergo malignant change.

Some type of surgical approach is usually recommended for patients with occlusive renal artery disease.[11] We have emphasized renal-conserving operations, either through repair of the affected vessels, arterial grafting or, if the left renal artery is involved, splenorenal arterial anastamosis. Nephrectomy is reserved primarily for patients with severe renal atrophy. Consideration should be given to the surgical risks involved, since in many patients the renal artery disease is part of widespread arteriosclerosis, carrying with it the threat of serious complications during the postoperative period. The fact that the hypertension of occulsive renal artery disease can respond to the usual antihypertensive drugs, makes operation less urgent and allows for the successful treatment of many a patient too ill to undergo surgery.

Few surgical sympathectomies are being done now because most hypertensive patients can be treated successfully with antihypertensive drugs. Currently, this treatment is reserved for those patients who either cannot or will not take antihypertensive drugs. Selection of patients who will respond significantly is no better than it ever was. Only about one-quarter of the patients operated upon can be expected to have a reasonable reduction in arterial pressure 6 months or more after operation. The fact that the effectiveness of chlorothiazide alone is said to be enhanced by sympathectomy has led to some feeling that operation should be performed first and then followed by the administration of oral diuretics. It should be stressed that as yet no report has been published describing responsiveness to chlorothiazide in a group of hypertensive patients before and after sympathectomy.

Implications of Responses to Antihypertensive Drugs

So little is know of the mechanisms whereby hypertension is maintained, that it is not surprising that drug treatment is imprecise. Yet, nonspecific though these medicines may seem, responses to them give some indications of their mechanisms. The fact that most hypertensive patients respond to drugs that affect the central and/or autonomic nervous system emphasizes the importance of neurogenic reflexes in the maintenance of hypertension. Presently, we know only 4 conditions in which hypertension seems to be neurogenic: brain tumor, acute porphyria, bulbar poliomyelitis, and paraplegia. Yet, responses to the available antihypertensive drugs suggest that other examples of hypertension are neurogenically maintained. For instance, patients with renal hypertension respond satisfactorily to ganglioplegic drugs and reserpine. This result might not have been anticipated, since the basis of renal hypertension probably is the renin-angiotensin system and angiotensin responsiveness is increased by ganglion blockade. However, McCubbin, Green and Page[12] have shown in chronic renal hypertensive dogs that there is resetting of the carotid sinus baroceptor mechanism. This suggests a neurogenic maintenance of hypertension that is hormonally initiated. The relationship between angiotension and increased vasomotor tone can only be validated when reliable methods are available for measurement of blood levels of renin and/or angiotensin.

The early effects of chlorothiazide suggest an interplay between the intravascular volume and neurogenic tone. Hemorrhage in dogs results in increased vasomotor outflow and this explains augmented responsiveness to ganglion-blocking drugs following blood loss. Thus, the early potentiating effect of chlorothiazide on responses to ganglioplegic drugs and reserpine seems due to oligemia and the associated increase in sympathetic activity. The fact that blood volume is normal in uncomplicated hypertension does not eliminate the possibility that a decrease in intravascular volume modifies the mechanisms maintaining hypertension. This position can be examined further when methods for measuring vasomotor outflow in man are available.

Summary

Use of antihypertensive drugs can reverse malignant hypertension and prolong life. A much longer time must elapse before an evaluation of treatment of "benign" essential hypertension can be made. Although treatment is not indicated in all hypertensive patients, it should be used in those with complications of arteriolar or arterial disease and in those who seem likely to develop such complications. Most antihypertensive drugs

act on the central and/or autonomic nervous system. This suggests a greater participation of neurogenic mechanisms in the maintenance of hypertension than we recognize clinically.

HARRIET P. DUSTAN, M.D.
Staff Member
Research Division
Cleveland Clinic Foundation, and
Frank E. Bunts Educational Institute
Cleveland, Ohio

REFERENCES

1. Keith, N. M., Wagener, H. P., and Barker, N. W.: Some different types of essential hypertension: Their course and prognosis. Am. J. Med. Sc. 197: 332, 1939.
2. Dustan, H. P., Schneckloth, R. E., Corcoran, A. C., and Page, I. H.: Effectiveness of long-term treatment of malignant hypertension. Circulation 18: 644, 1958.
3. Paton, W. D. M.: Pharmacology of ganglion-blocking agents. *In* Hypertension: First Hahnemann Symposium on Hypertensive Disease, J. H. Moyer, Ed. Philadelphia. W. B. Saunders Co., 1959, pp. 365-375.
4. McCubbin, J. W., and Page, I. H.: Do ganglion-blocking agents and reserpine affect central vasomotor activity? Circulation Research 6: 816, 1958.
5. Page, I. H., and Dustan, H. P.: New, potent antihypertensive drug: Preliminary study of [2-(octahydro-1-azocinyl)-ethyl] -guanidine sulfate (guanethidine). J.A.M.A. 170: 1265, 1959.
6. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L.: Darenthin, hypotensive agent of new type. Lancet Vol. II, no. 7089: 17, 1959.
7. Dustan, H. P., Cumming, G. R., Corcoran, A. C., and Page, I. H.: Mechanism of chlorothiazide-enhanced effectiveness of antihypertensive ganglioplegic drugs. Circulation 19: 360, 1959.
8. Freis, E. D.: Effects of salt and extracellular fluid depletion on vascular responsiveness with particular reference to chlorothiazide. *In* Hypertension, Vol. VII: Drug Action, Epidemiology and Hemodynamics. Proceedings of the Council for High Blood Pressure Research, American Heart Association, November 1958, p. 6.
9. Dublin, L. I., Lotka, A. J., and Spiegelman, M.: Length of Life: Study of the Life Table, revised ed. New York, Ronald Press, 1949, pp. 178-180.
10. Bechgaard, P., Kopp, H., and Nielsen, J.: One thousand hypertensive patients followed from 16-22 years. Acta med. scandinav., suppl. 312: 175, 1956.
11. Page, I. H., Dustan, H. P., and Poutasse, E. F.: Mechanisms, diagnosis and treatment of hypertension of renal vascular origin. Ann. Int. Med. 51: 196, 1959.
12. McCubbin, J. W., Green, J. H., and Page, I. H.: Baroceptor function in chronic renal hypertension. Circulation Research 4: 205, 1956.

Coming Soon . . .

SYMPOSIUM ON CONGESTIVE HEART FAILURE

A symposium on fundamental and clinical features of congestive heart failure has been published in the January, February and March, 1960, issues of *Circulation*. This symposium, the first of a series of monographs, will soon be available at the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Many of these outstanding articles will be of special interest to physicians concerned with the recent progress in cardiology:

Starling and the Concept of Heart Failure, *Sir George Pickering*

Hemodynamic Aspects of Congestive Heart Failure, *L. N. Katz, H. Feinberg* and *A. B. Shaffer*

Metabolism of the Heart in Failure, *William H. Danforth, F. B. Ballard, K. Kako, J. D. Choudhury,* and *R. J. Bing*

Kidney in Congestive Heart Failure, *A. C. Barger*

Clinical Management of Congestive Heart Failure, *Herrman L. Blumgart* and *Paul M. Zoll*

Correction of Hyponatremia in Congestive Heart Failure, *E. Hugh Luckey* and *Albert L. Rubin*

Clinical Consideration of Cor Pulmonale, *Réjane M. Harvey* and *Irené Ferrer*

Pediatric Aspects of Congestive Heart Failure, *Alexander S. Nadas* and *Anna J. Hauck*

Congestive Phenomena Occurring in Pregnant Women with Heart Disease, *C. Sidney Burwell* and *James Metcalfe*

Unusual Causes of Heart Failure, *Howard B. Burchell*

Rehabilitation in Congestive Heart Failure, *Howard A. Rusk* and *Menard M. Gertler*

American Heart Association Monograph Series No. 1